**UPDATE ON IRIS PROGRAM ACTIVITIES** August 18, 2011

## Improvements to IRIS Process

The IRIS Program has had more major assessments in play during 2011 than in any other year in the history of the IRIS Program. This is due, in large part, to changes made to the Program over the past few years. In May 2009, EPA announced a new IRIS assessment development process to streamline, strengthen, and improve transparency within the program while ensuring the highest level of scientific quality and integrity and a renewed commitment to rigorous independent peer review. Since that time, EPA has completed 17 assessments, more than the number of assessments that were completed in the previous four years. The IRIS backlog has been significantly reduced, and the Agency has about 70 assessments in the IRIS process at various stages at this time. In FY 2010, EPA completed 10 IRIS assessments and released nine for public review and comment and external peer review, seven of which were major assessments.

In FY 2011, we anticipate completing nine assessments, including several major assessments (bolded assessments have already completed milestones):

- Urea
- **Trichloroethylene**
- Hexachloroethane
- Dichloromethane
- Platinum
- Tetrahydrofuran
- Trichloroacetic acid
- Ethylene oxide
- **Tetrachloroethylene**

Additionally, we anticipate releasing eight draft assessments for public review and comment and external peer review, including:

- Acrylonitrile
- 1,4-dioxane (inhalation)
- **Libby asbestos**
- Benzo(a)pyrene
- Vanadium pentoxide
- N-butanol
- Biphenyl
- **Polychlorinated biphenyls (PCBS), noncancer**

Note upcoming milestones in FY11 for several major assessments (**bolded** above).

Finally, in FY 2011 we sent 14 draft assessments for Agency review (Step 3) – another record – and seven for interagency science consultation (Step 3) prior to external peer review. We also sent nine draft assessments for final Agency and interagency review (Step 6) prior to posting on the database.

Continually improving IRIS is an ongoing priority for the Agency, and efforts are underway to further strengthen and streamline this important program. For example, in response to recent recommendations by the National Academy of Sciences, EPA is making changes in the way draft IRIS assessments are developed. We will:

- Rigorously edit assessment documents to reduce text volume and address redundancies and inconsistencies;
- Build on existing IRIS guidelines to enhance the clarity and transparency of data evaluation and presentation of findings and conclusions;
- Consolidate related discussions to eliminate redundancies and increase the use of tables and figures to improve communication of information;
- Provide a fuller discussion of methods and concise statements of the criteria used to exclude or include studies for hazard evaluation and derivation of toxicity values; replace text study descriptions with standardized evidence tables that provide the methods and results of each study for all health outcomes;
- Use uniform approaches to thoroughly evaluate the strengths and weaknesses of critical studies, summarize findings in tables, and clearly articulate the rationale for selecting studies used to calculate toxicity values; and
- Describe the various determinants of weight of evidence to promote understanding of the elements that were emphasized in synthesizing the evidence.

EPA is also working with the Science Advisory Board to develop a dedicated IRIS Review Committee that will exclusively focus on the quality, transparency and scientific rigor of IRIS assessments. A clear benefit of this standing committee is that it will provide consistency in assessment reviews and can serve as an additional quality control measure, ensuring that any IRIS process improvements are successfully implemented and truly enhance the program. EPA will also add an early peer consultation step to the IRIS draft development process for major assessments. This will enhance the input from the scientific community as assessments are designed. Overall, by taking these steps, EPA believes we will be able to even further strengthen the IRIS Program.

**Chromium VI**

EPA initiated a reassessment of the health effects of chromium VI in the fall of 2008 in response to the release of the National Toxicology Program (NTP) study that demonstrated clear evidence of the carcinogenicity of ingested hexavalent chromium in laboratory animals. This assessment was created in collaboration with CalEPA, NJDEP, ATSDR, and EPA's OPP. The draft assessment includes an RfD, a cancer descriptor of "likely to be carcinogenic" to humans by all routes of exposure, a determination that chromium VI is carcinogenic by a mutagenic mode of action, and an oral cancer slope factor derived using a low-dose linear approach. The draft assessment underwent independent external peer review in May 2011. A number of commenters made presentations on ongoing unpublished research to the expert panel at the public peer review meeting. The commenters indicated to the panel that their research on the mode of carcinogenic action and bioreductive capacity of the GI tract would influence the outcome of the assessment. The final peer review report was posted on IRIS in July 2011.

Major comments received from peer reviewers on the draft health assessment included:

- A number of comments were received on the derivation of the RfD which focused on the consideration of other endpoints for defining the critical effect and the need to consider bioavailability to a greater extent in the derivation of the RfD.
- The majority of reviewers stated that several lines of evidence were consistent with a non-mutagenic MOA, which is also consistent with a threshold mechanism and which argues against developing an oral cancer slope factor from the NTP tumor data using a linear approach. These lines of evidence as stated by the reviewers include: 1) the NTP (2008) animal data showed evidence of a cancer increase only at the highest doses, 2) there is likely to be a dose at which the bioreductive capacity of the GI tract would be overwhelmed before toxicity would occur, and 3) the more recent ACC studies [unpublished] demonstrate hyperplasia would occur prior to (or maybe a precursor of) tumor formation.
- Several reviewers indicated that an analysis of the inhalation database, along with the oral database, might prove useful for informing the mode of action.
- Several reviewers recommended that EPA wait for the publication of the new ACC-sponsored research before finalizing the assessment.

**Options for next steps**

**Option 1**: Revise the assessment incorporating the peer review comments.

- Timeline: 3 to 4 months for revisions, could be posted on the database in 2nd QTR FY12
- May require additional peer review due to significant changes

**Option 2**: Place the assessment on hold while waiting for publication of the ACC-sponsored research.

- Timeline: hold could last 10 to 12 months assuming publication of all studies by June 2012 (6 months after journal submission).
- Assessment would essentially start from the beginning of the IRIS process at that time; however, time for completion of the revised draft could be significantly reduced.
- Estimate of completion date – 1st QTR FY14

**Dioxin**

In May 2010, ORD released for public review and comment and external peer review a draft report titled "EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments" ("Reanalysis") that responds to the recommendations and comments included in the National Academy of Sciences' (NAS) 2006 review of EPA's 2003 draft dioxin assessment. EPA's Science Advisory Board (SAB) is currently reviewing the draft Reanalysis; however, they released a draft review report in May 2011.

In their draft review, the SAB:

- Found that the draft reanalysis was clear, logical and responsive to many of the recommendations by the NAS, and they commended the EPA for the comprehensive and

rigorous process that was used to identify, review and evaluate the scientific literature, adding that the criteria for study selection have been clearly articulated, well justified, and applied in a scientifically sound manner;
- Agreed with EPA's choice of two epidemiology studies as co-critical studies to support the oral reference dose;
- Agreed with ORD's choice of model for dose metric calculations; and
- Agrees with EPA's classification of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) as carcinogenic to humans

The SAB also advised EPA to conduct a sensitivity analysis and provide a discussion of evidence of possible modes of action that include both linear and nonlinear alternatives for the cancer endpoint.

EPA expects to receive the final SAB report at the end of August. We do not anticipate major changes from the draft review report. To that end, EPA will complete the noncancer portion of the Reanalysis and post the final assessment to the IRIS database by the end of January 2012. This will be a significant milestone for the Agency, representing the first time ever that EPA has set an oral reference dose for dioxin. EPA will then address the SAB comments related to the cancer portion of the reanalysis and will complete that portion of the assessment as expeditiously as possible.

**Arsenic**

EPA's draft IRIS assessment for inorganic arsenic (cancer) has been developed based upon the recommendations by the National Academy of Sciences and EPA's Science Advisory Board. ORD has revised the report according to recommendations from the Science Advisory Board received in early March 2011. Briefly the following revisions have been made to the assessment. Major Revisions in Response to SAB (2011) review:

1. *SAB recommended stating the factors used to evaluate and present the epidemiology studies.*
   EPA has systematically added text in the Toxicological Review to transparently indicate how each of the epidemiology studies were evaluated based upon the SAB recommended factors.
2. *SAB supported using the Taiwanese dataset (Chen et al. 1988, 1992; Wu et al., 1989), but recommended additional sensitivity analyses and support for modeling assumptions.*
   EPA has provided additional sensitivity analyses to the Toxicological Review. EPA has added text in the Toxicological Review to provide a transparent rationale and scientific support for the modeling assumptions.
3. *SAB recommended adding an addendum to describe major epidemiology studies published since 2007 (i.e., the literature search cutoff date) that could substantially impact the cancer risk estimate.*
   EPA has added an appendix of major epidemiology studies published since 2007, of which only two studies (Chen et al., 2010a, 2010b) could impact the cancer risk estimates.

4. *Public commenters have asked EPA to update the literature search to include studies published since 2007 (i.e., the literature cutoff date)*

   EPA used the Health and Environmental Research Online (HERO) to complete a literature search through May 2011. This search yielded an additional 282 articles that would be considered in a future arsenic assessment. These studies are not included in the final draft nor have they been fully reviewed by EPA, but the literature search product is available on the HERO database. We expect criticism for not considering these studies in the final assessment.

The revised assessment is ready to submit to Final Agency/interagency review which would be followed by posting the final assessment to the IRIS database. Subsequent to posting, we propose that EPA acknowledge the availability of new science and commit to immediately begin a new IRIS assessment, anticipated to be completed in 23 months. The SAB mentioned putting the noncancer and cancer assessments together in the future and their willingness to review the combined assessment.

**Methanol**

In June 2010, EPA announced that the IRIS methanol (cancer and noncancer) assessment was on hold due to a report from the National Toxicology Program (NTP) outlining a review of research on methanol conducted by the Ramazzini Institute. The NTP report recommended further pathology reviews be carried out to resolve differences of opinion between NTP scientists and the Ramazzini Institute. This study has no bearing on the evaluation of non-cancer health effects for methanol. Therefore, the non-cancer evaluation for methanol was released for a second round of public comment in April 2011, a listening session was held in May and the external peer review meeting was held on July 22, 2011. The final peer review report is expected in August. The cancer evaluation remains on hold as we await the findings from the ongoing pathology review that EPA is jointly sponsoring with NIEHS which includes a complete evaluation of the methanol cancer data.

**Formaldehyde**

In June 2010, the external review draft was submitted for public comment and review by the National Academy of Sciences (NAS). The NAS released their report to the public on April 8, 2011. The formaldehyde team is evaluating the NAS recommendations and public comments and revising the formaldehyde assessment accordingly. Projected estimates for completion of the revised draft and next steps are currently under discussion.

**Other Topics**

**Halogenated platinum salts**

- currently in Final Agency/interagency review prior to posting in FY11
- halogenated platinum industry has asked that the assessment not be finalized

**Acrylonitrile**

- currently available for public comment; recently held listening session
- external peer review meeting tentatively scheduled for September
- subject of comments at the House IRIS hearing

**Interagency review**

- pace of reviews
- OMB and NASA issues
- recent improvements to process

**Ramazzini update**

- recently received draft pathology workgroup reviews for methanol, MTBE and ETBE
- waiting for one more draft report on acrylonitrile and vinyl chloride
- joint communication effort with NIEHS